Image-Guided Intervention Workshop

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Bioscience and Engineering in NASA's Office of Biological and Physical Research

Prior to January 14, 2004

- Physical Sciences separate from Fundamental Biology and Bioastronautics
- Emphasis on fundamental knowledge for spaceflight
- Preliminary steps toward organizing a BIoScience and ENgineering (BISEN) organization within the physical sciences managed at GRC
- BISEN goal was delivery of advanced hardware and computer simulations to enable human exploration of space with implementation via cross-discipline and cross-center teams
- GRC had a heritage of this from work with bioreactors and the Light Microscopy Module (LMM)
- GRC had a heritage of working with other federal agencies

Bioscience and Engineering in NASA's Office of Biological and Physical Research

After January 14, 2004

- NASA is rapidly implementing the President's vision
- Fundamental research has been greatly reduced or eliminated.
- Focus is only on solving problems preventing long duration human spaceflight
- Cross-disciplinary and cross-center teams appear to be more important than ever
- NASA is leveraging effort by drawing in any expertise extant in the external community

Example: Digital Astronaut Program

Bioscience and Engineering in NASA's Office of Biological and Physical Research

OBPR and Image Guided Interventions

- Operationally define "intervention" as any action taken that deviates from the nominal mission timeline
- Not all interventions require imagery
- NASA is still defining work that must be performed; collaboration with external groups is encouraged
- Problems to solve are outlined in the Bioastronautics Critical Path Roadmap (http://criticalpath.jsc.nasa.gov)

This presentation will address current collaborative organizations

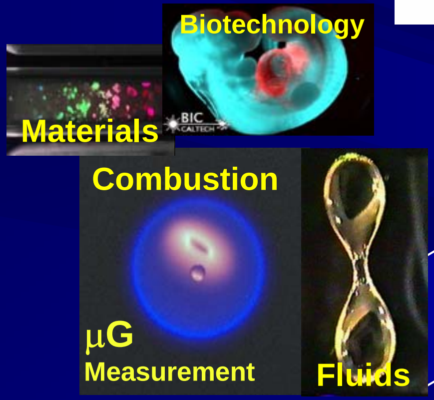
- Illustrate how NASA has done business in the past
- Outline important research areas
- Suggest vehicles and research for future collaborative efforts

GRC BioScience and Engineering

Goal 4 *Explore the fundamental principles of physics, chemistry and biology through research in the unique natural laboratory of space*

Goal 9 *Extend the duration & boundaries of human space flight to create new opportunities for exploration & discovery*

- ✓*Biological and Physical Research Rack (BPRR)*
- ✓*Improved Science Imaging*
- ✓*Advanced diagnostics*
- ✓*Improved cell culturing systems*



Enabling Technology for Fundamental Research

Increasing Technology Readiness Level

- ✓*Human Physiology*
- ✓*Miniature, low power, reliable Vehicle & Human Space Systems*
  - ✓*Biomedical diagnostics & environmental sensors*
- ✓*Radiation, bone loss countermeasures*
- ✓*Medical applications*

The John Glenn Biomedical Engineering Consortium

- ✓*Biomedical Issues*
  - •*Medical diagnostics*
  - •*Medical Treatment*
  - •*Countermeasures*

NASA BioScience & Engineering Institute

- ✓*BioMEMS*
- ✓*Bio materials*
- ✓*Transport phenomena in biology & devices*
- ✓*Lab-on-chip*
- ✓*Molecular Nanosystems*
- ✓*Tissue BioScience and Engineering*

- ✓*Fluid Modeling of Physiological, Vehicle & Cell Culturing Systems*
- ✓*Low gravity effects on fluid to cell environment*
- ✓*Fluids & combustion sensor technology for biomedical & advanced life support*
- ✓*1g g-jitter measurement of bioreactors*

GRC BioScience and Engineering Program Objective

Objective

- Leverage (use existing science knowledge & capabilities) and pursue (expand existing knowledge & capabilities) advances in the physical sciences and engineering to enable similar advances in reduced-gravity fundamental biology (cell, plant, animal), biomedical (human physiology & life support) and biotechnology (cellular & protein crystal growth) research and enabling hardware/software.

Distinction between BioScience Discipline & Microgravity Discipline Specific Research

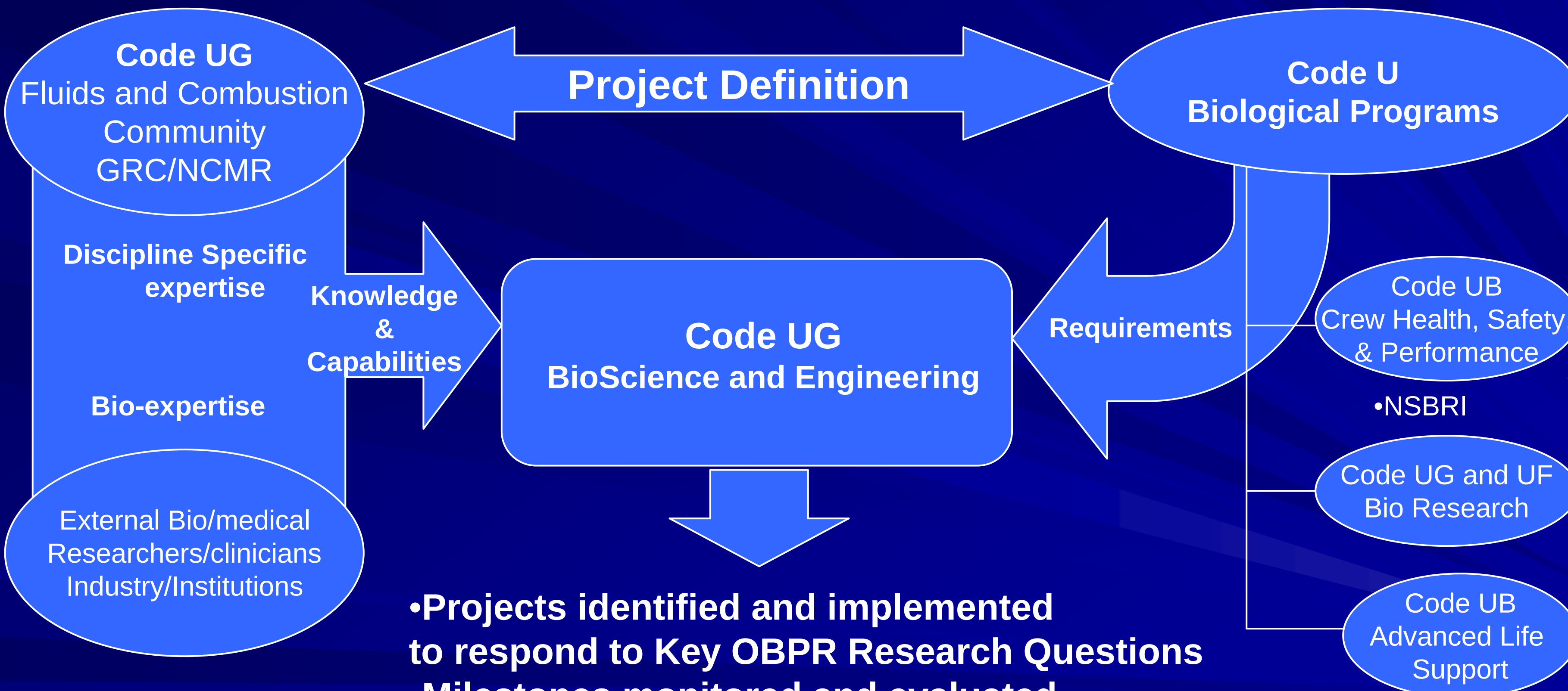
- BioScience project/study selection and success requires the close collaboration and participation with/by biomedical and/or biotechnology researchers.

Discipline Researcher + Bio-Researcher = BioScience

BioScience and Engineering Program Objective

GRC/Code UG Working Model

Couple existing reduced gravity researchers with fundamental biology, biomedical and/or biotechnology researchers and apply these capabilities to Code UG BioScience & Engineering Research.



- **Projects identified and implemented to respond to Key OBPR Research Questions**
- **Milestones monitored and evaluated**

Project Definition - Identify what needs to be done?

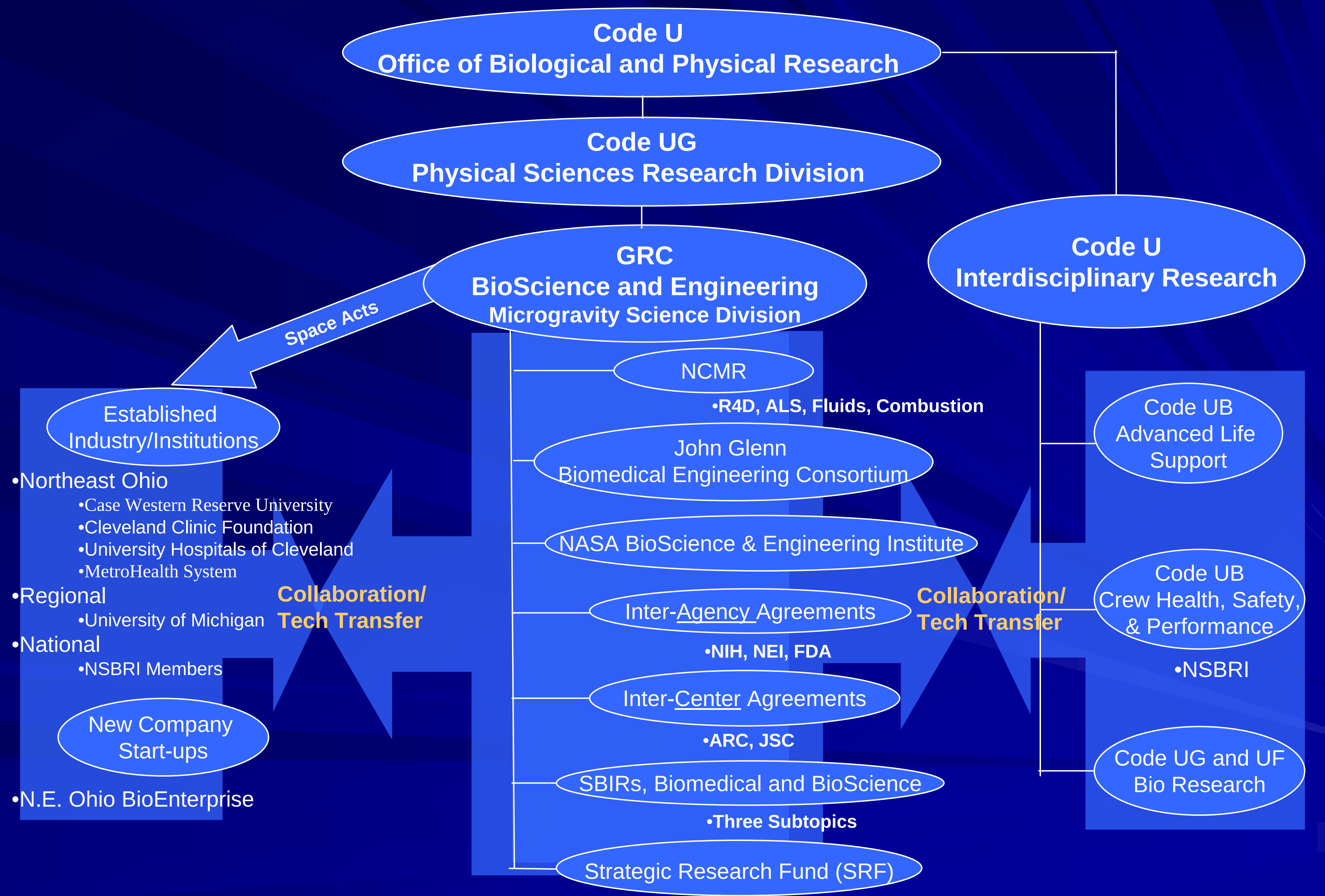
Some of the most challenging questions involve life and biological systems that depend crucially on the interplay between biological and physicochemical processes.

- life support systems
- implementation of medical countermeasures
- human physiological response to low gravity

Because of the complexity of the problems, the interactions between the physical and biological components of these systems, and **because of the need to fulfill specific mission requirements, it is essential that the identification, assignment and conduct of the research be directed to provide NASA with the information needed to accomplish its mission**

Program Content

BioScience and Engineering Program at GRC



GRC Core OBPR Sponsored Program

NASA John Glenn Biomedical Engineering Consortium – 10 projects

- Projects funded to address risks identified in the Bioastronautics Critical Path Roadmap

NASA BioScience and Engineering Institute – University of Michigan

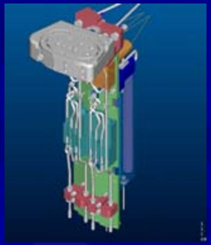
- To enable world-class research, development, U.S. technology transfer, and education in BioScience and Engineering related to NASA's overall missions

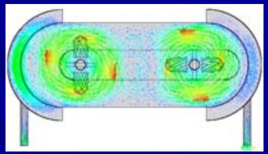
Enhanced National Center for Microgravity Research (NCMR)

- Fluids and transport knowledge for advanced life support, physiological systems modeling, physiochemical processes

Interagency Agreements

- HQ-sponsored with NIH-NEI and FDA
- Development of new proposals for consideration





Inter-center Collaborations

- ARC: Fundamental Space Biology
- JSC: Bioastronautics and Cellular Biotechnology

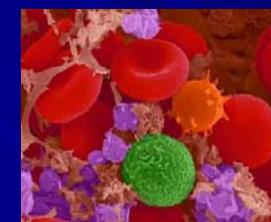
Small Business Innovative Research Program (SBIR) Topics

- Biomedical R&D of Noninvasive, Unobtrusive Medical Devices for Future Flight Crews
- BioScience and Engineering
- Nanoscale Self Assembly using Biological Molecules

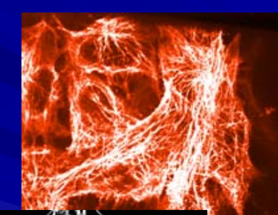
Additional GRC Activities

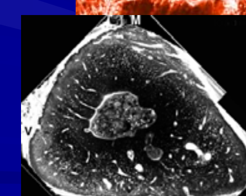
- Eleven GRC internally funded studies in bio-related research - SRFs
  - Fluids Modeling, Sensors, Diagnostics/imaging

- Five GRC Commercial Technology Office funded bio projects
  - Telemetry/data processing,Sensors, Materials

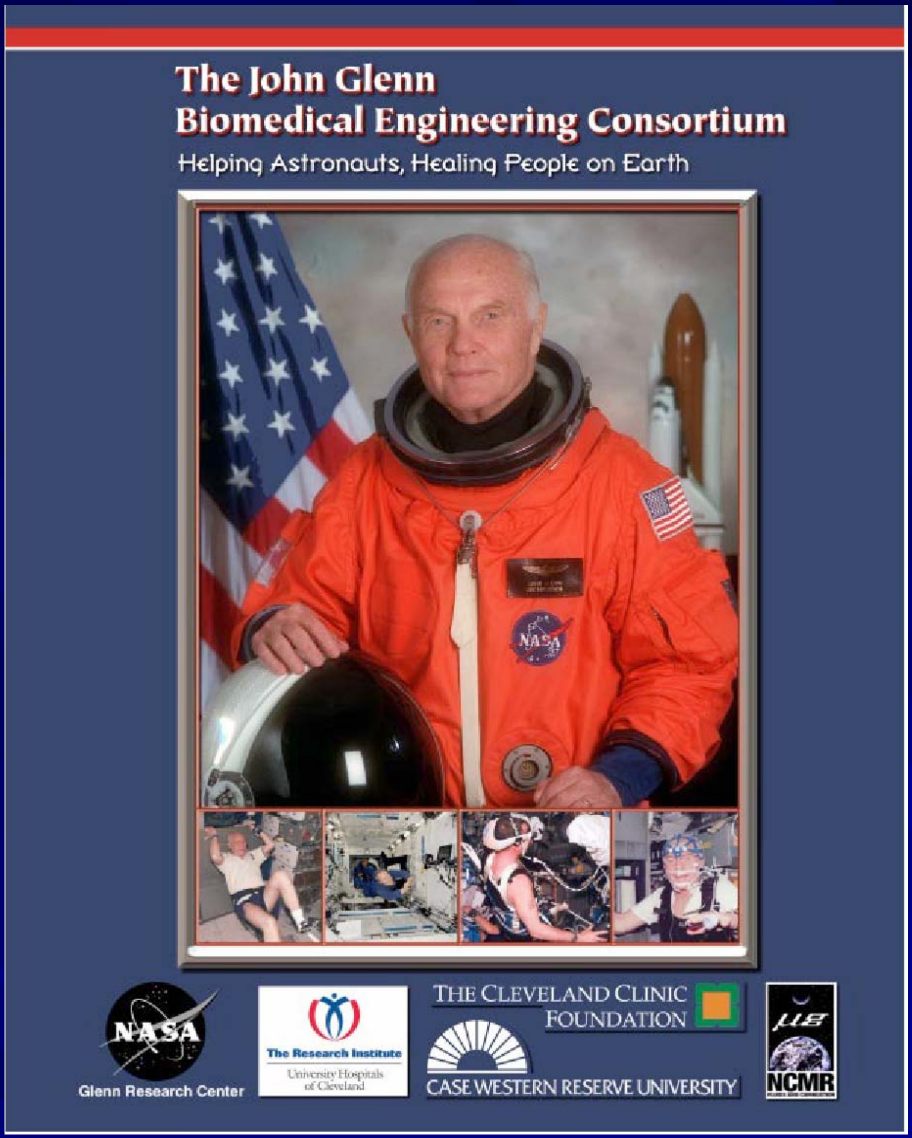


- Thirteen current Space Act Agreements for bio-related work
  - CWRU, CCF, UHC, seven commercial companies
- Limited proposals to NIH, DOD
  - Partnering with principal investigators
- Collaboration with BioEnterprise to create, attract and accelerate bioScience start-up companies across Northeast Ohio
  - Space Act Agreement –
    - Assessment of proposed technologies and concepts
    - Sharing of expertise, facilities and equipment





- Employee training / education through short courses and graduate degrees



JOHN GLENN BIOMEDICAL ENGINEERING CONSORTIUM

Inter-institutional research and technology development, beginning with **ten projects** in FY02 that are aimed at applying local expertise in fluid physics and sensor development to mitigate the risks of space flight on the health, safety, and performance of astronauts.

It is anticipated that several new technologies will be developed that are applicable to both medical needs in space and on earth.

John Glenn Biomedical Engineering Consortium

Members: Case Western Reserve University (CWRU)
Cleveland Clinic Foundation (CCF)
University Hospitals of Cleveland (UHC)
National Center for Microgravity Research (NCMR)
NASA Glenn Research Center (GRC)

Focus: Interdisciplinary research leveraging GRC expertise in fluid physics and sensor technology to mitigate critical risks to crew health, safety, and performance identified in the Bioastronautics Critical Path Roadmap

Sponsor: Office of Biological and Physical Research (OBPR)

Resources: OBPR Funding - $7.5 M over three years
Member personnel, facilities, capabilities, leveraging and in-kind contributions

THE CLEVELAND CLINIC FOUNDATION

CWRU

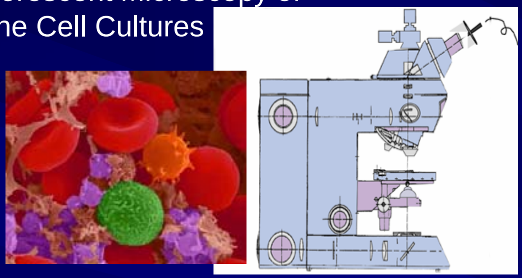
NASA

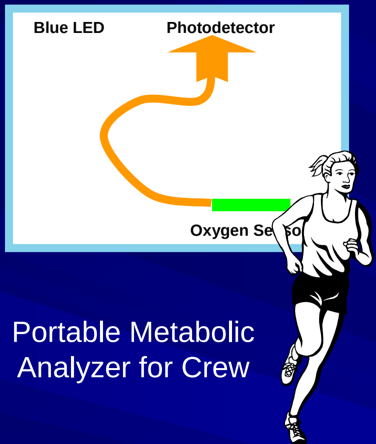
NCMR
FLUIDS AND COMBUSTION

The Research Institute
University Hospitals of Cleveland

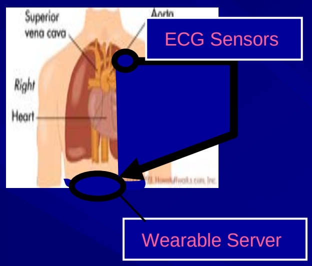
Biomedical Engineering Consortium Projects

Fluorescent Microscopy of Bone Cell Cultures



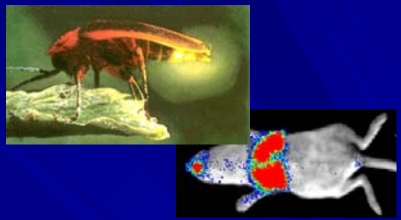


Portable Metabolic Analyzer for Crew

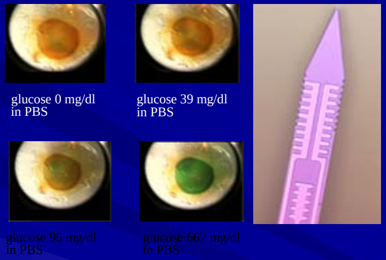


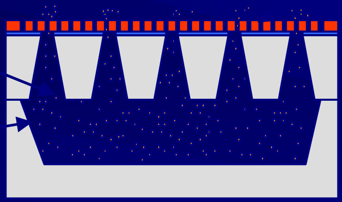
Detection and Web-based Reporting of Cardiac Dysrhythmia

Bioluminescent imaging for radiation dosimetry

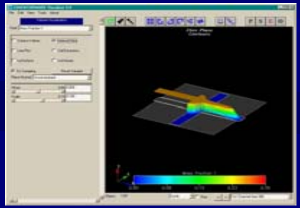


Microminiature Glucose Sensor

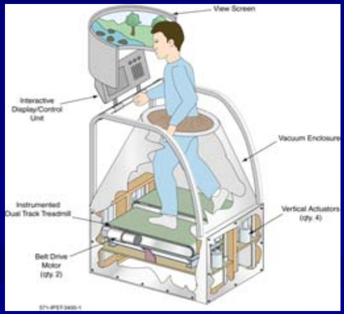




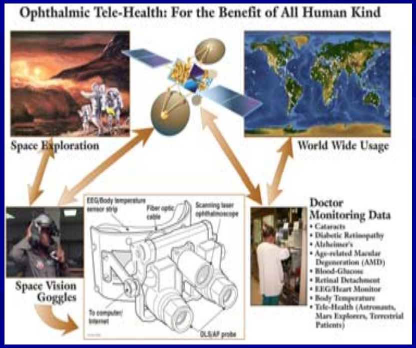
Controlled-Release Microsystems for Pharmacological Agent Delivery



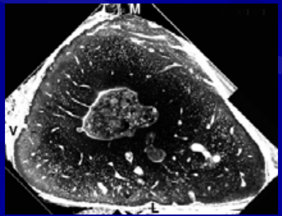
Rapid Design and Simulation Tools of Space-bound Biochips



Virtual Reality Dual-Action Treadmill for Improved Neurovestibular Adaptation



Non-invasive Eye Measurements to Reveal the Body's Health



Acoustically Induced Micro-damage to Prevent Bone Loss.

JGBEC Projects

Wilson, CWRU Co-I: UH	In-Vivo Bioluminescent Molecular Imaging with Application to the Study of Secretory Clusterin, a Potential Biodosimeter during Space Exploration
Ansari, GRC Co-I: UH	Integrating Non-invasive Technologies to Enable Effective Countermeasures During Prolonged Space Travel
Gratzel, CWRU	Micro-miniature Sensing Platform For Painless, Infection-Free, And Continuous In Vivo Monitoring Of Glucose And Electrolytes Of Astronauts
Knothe, CCF Co-I: CWRU, GRC	Development of a “Decompression Chamber” to Prevent Loss of Bone in Space through Exogenous Application of Acoustic Energy
York, GRC Co-I: CWRU	Remote and On-board Detection, Diagnoses and Treatment of Serious Cardiac Dysrhythmias
Dietrich, GRC Co-I: NCMR, UH	Development of a Portable Metabolic Measurement Device
Roy, CCF Co-I: CWRU, GRC	Controlled-release Microsystems for Pharmacological Agent Delivery
Chait, GRC Co-I: NCMR, CWRU	Rapid Design and Simulation Tools for Space-Bound BioChip Devices
D'Andrea, CCF Co-I: GRC	An Instrumented, Dual-Track, Actuated Treadmill in a Virtual Reality Environment as a Countermeasure for Neurovestibular Adaptations in Microgravity
Zimmerli, GRC Co-I: CCF	Confocal And Two-Photon Microscopy For The Assessment Of Countermeasures In Bone Loss, Hematology, And Immunology

Integrating Non-Invasive Technologies to Enable Effective Countermeasures During Prolonged Space Travel – Rafat Ansari, GRC

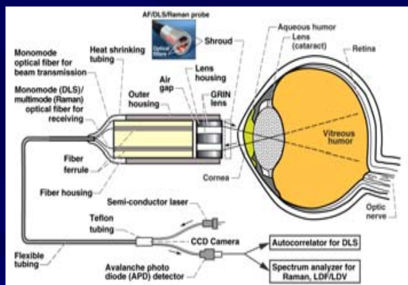
Experimental Rack On-board the KC-135 for Ocular Blood Flow Experiment

Ocular Blood Flow Monitoring in "0 g" in a test subject (RRA) On-board the KC-135 airplane

- Detection of Cataracts and Glaucoma
- Monitoring of Blood Glucose (Diabetes & Diabetic Retinopathy)
- Monitoring of Oxygen
- Brain physiology
- Ocular and nervous system circulatory physiology

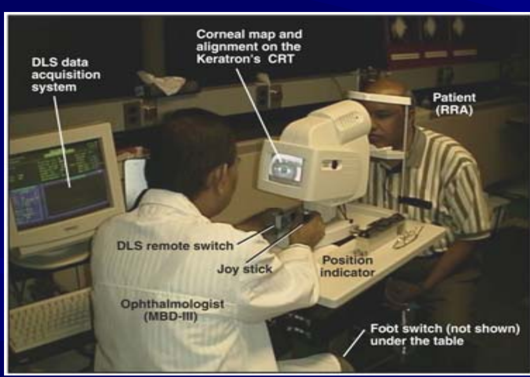
The Eye as a Window to the Health of Our Bodies

NEI/NIH Interagency Agreement



Patent # 5973779 Ansari and Suh, 1999

A prototype instrument that looks into the eye and gathers data on the subject's health, and then sends it to the laptop computer for analysis.



Clinical Trials at NIH

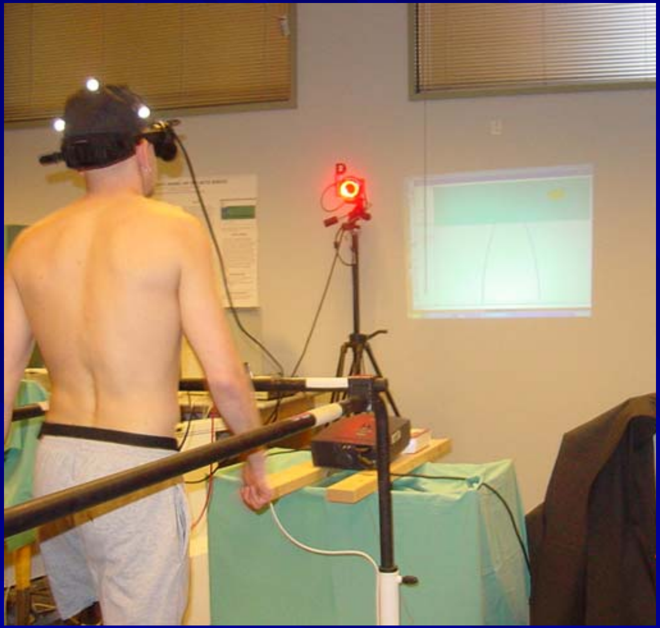
Modular Design

- Detection of Cataracts and Glaucoma
- Monitoring of Blood Glucose (Diabetes & Diabetic Retinopathy)
- Monitoring of Oxygen
- Brain physiology
- Ocular and nervous system circulatory physiology

A Dual-Track Actuated Treadmill in a Virtual Reality Environment: A Countermeasure for Neurovestibular Adaptation in Microgravity – Susan D'Andrea, CCF

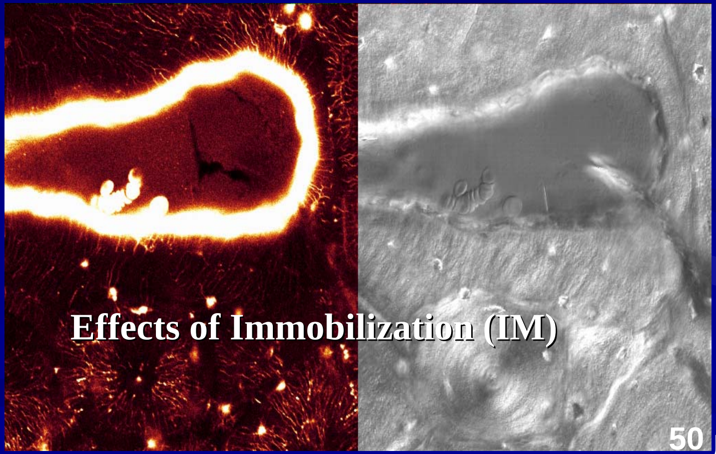
- To design and develop an exercise countermeasure
  - Challenge the postural control system
  - Exercise balance and locomotor reflexes
  - Alleviate adverse adaptations to neurovestibular system
- Address multiple physiological systems
  - Neurovestibular
  - Musculoskeletal
  - Cardiovascular

Subject on treadmill with VOR measurement


Visual Display with Treadmill

Acoustically Induced Microdamage to prevent Bone Loss –
Ulf Knothe, CCF

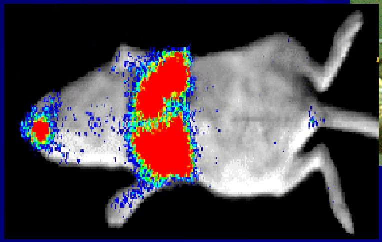
- Identify the bandwidth and application regime necessary to:
  - ➢ enhance fluid flow and mass transport through bone matrix
  - ➢ produce low-level, diffuse microdamage similar to that ensuing from normal physiological activity on Earth
- Design an experimental device and to test its efficacy in the hind limb suspension model of the rat
- Build the countermeasure device for space application.

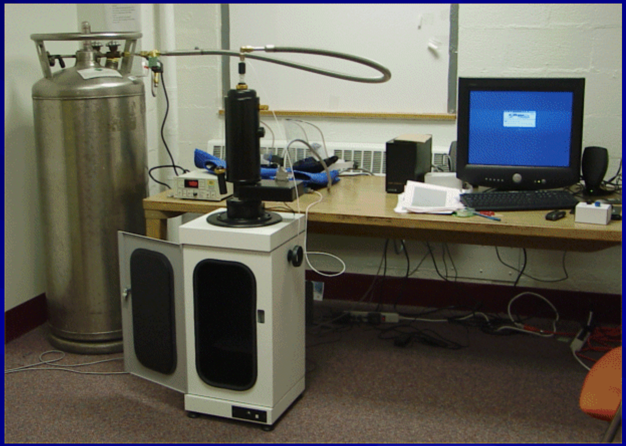


50 µm

In Vivo Bioluminescent Molecular Imaging with Application to the Study of Secretory Clusterin, a Potential Biodosimeter During Space Exploration – David Wilson, CWRU

- Introduce luciferase gene from fireflies near a gene of interest in cells
- Luciferase acts as a reporter gene. It expresses luciferase protein whenever the gene of interest is expressed.
- Luciferase protein and its substrate luciferin create light
- Clusterin is secreted by cells in culture and animals following low levels of radiation





In vivo bioluminescence imaging system.

Clusterin biodosimeter will measure the biological effect of radiation exposure

Confocal and Two-Photon Microscopy for the Assessment of Countermeasures in Bone Loss and Immunology –

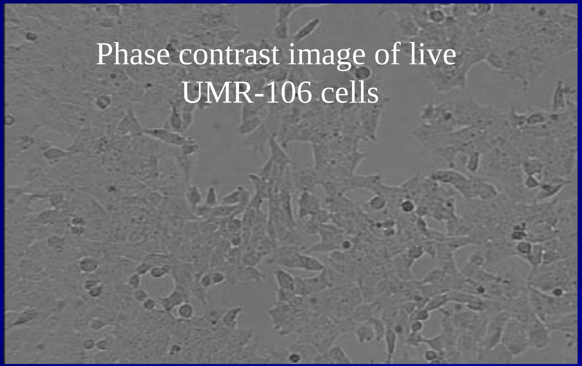
Greg Zimmerli, GRC

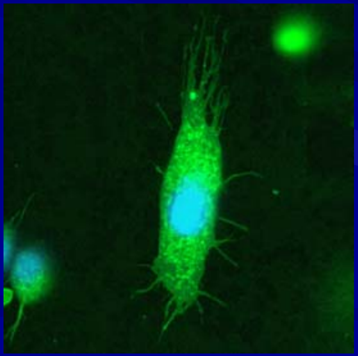
Goal: Use fluorescence microscopy techniques to assess, at a cellular level, the effectiveness of countermeasures (esp. bone loss)

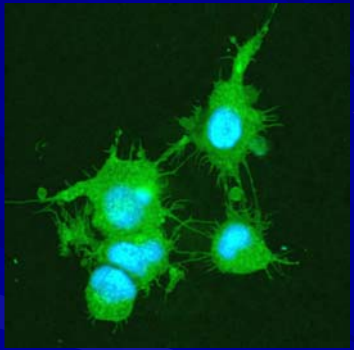
Method: Fluorescence microscopy techniques are being used as an assay for quantifying the response of cell cultures

- Fluorescence microscopy techniques:
  - Two-photon
  - Fluorescence Correlation Spectroscopy
  - Fluorescence Resonance Energy Transfer
  - Fluorescence Lifetime Imaging Microscopy

- Quantifying cellular response:
  - Cell proliferation,
  - Structure,
  - Protein associations


Phase contrast image of live UMR-106 cells





Two-photon images acquired in the NASA GRC Biophotonics lab of the UMR-106 osteosarcoma cells

<u>Possible</u> NASA/NIH Inter-Agency Agreement

Counteracting Bone and Muscle Loss and Understanding the Cardiovascular system through Clinical Testing and Computational Modeling

Computational Modeling of bone and cardiovascular system

- NASA-parallel computing
- NASA-soft tissue / materials characterization
- NASA-advanced fluid/solid interaction modeling
- CCF-musculoskeletal modeling
- CCF-Cardiovascular modeling

Experimental Modeling of bone and cardiovascular System

- NASA/Russian Crew Data On bone loss
- CCF-muscoskeletal research robot
- CCF-bed rest studies
- NASA-advanced control and sensor systems
- NASA/CCF-advanced imaging capabilities

Formation of an <u>Interdisciplinary Research Team</u> focused on specific terrestrial and space based health issues

OUTCOME 1: Sophisticated modeling of lower extremities including bone and cardiovascular system

OUTCOME 2: Fundamental understanding of bone loss mechanisms and mitigation strategies

OUTCOME 3: Optimized forms of exercise for astronauts and elderly to mitigate bone loss

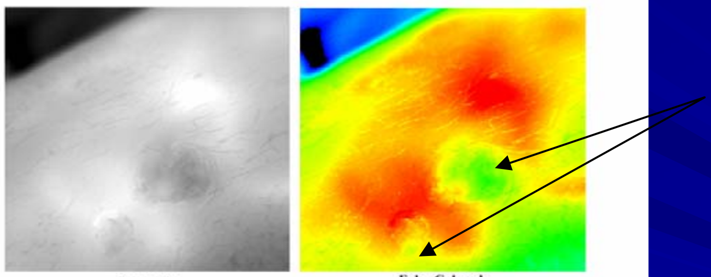
Multispectral Imaging for Medical Diagnosis

Medical Problem: Pyroderma Gangrenosum

Presents As: Large violaceous ulcers seen in most patients begin as sterile pustules or nodules that rapidly break down, eroding and undermining surrounding tissues. The expanding lesions thus have a pathognomonic rolled border They most often occur on the legs.

Question: Can infrared imagery predict ulcers before they erupt?

Lesions are colder than surrounding tissue. CCF clinicians were interested in applying the technique to detecting angiogenesis associated with malignancies, particularly of the colon



Grayscale: Lighter shaded areas correspond to increased surface temperature

False Colored: Green areas are lowest temperature, yellow to red colored areas correspond to increased surface temperature

Programmatic Problem: Cementing collaboration with research funds

NASA BioScience and Engineering Institute (NBEI)

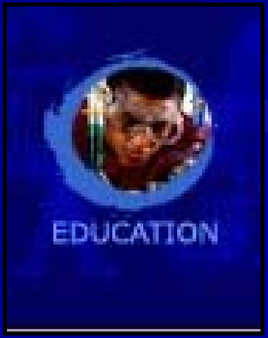
University of Michigan

Objective:

- Enable world-class research and development in bioscience and engineering related to NASA's overall missions with emphasis on human exploration and development of space

Approach:

- **Investigative effort organized into Research Themes and individual projects which includes education and outreach as an integral component. To align with NASA exploration priorities, areas of emphasis include:**
  - **Transport Phenomena in Biology and Devices**
  - **Tissue BioScience and Engineering**
  - **BioMEMS and Biomaterials**
  - **Molecular Biophysics and Bioengineering**



NASA BioScience and Engineering Institute (NBEI)

University of Michigan

X-ray image of rabbit lung partially filled with perfluorocarbon

An Earth-Based Model of Microgravity Pulmonary Physiology

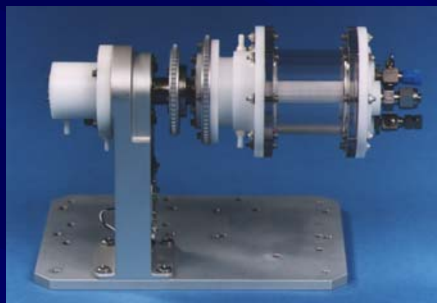
PI Ronald B. Hirschl, M.D.

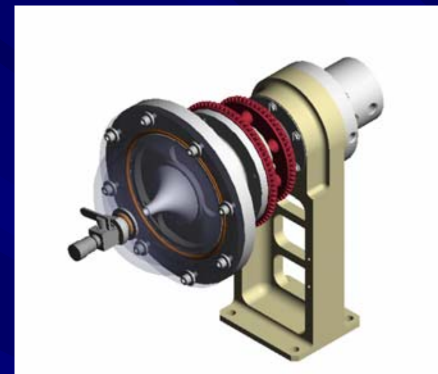
Research Details

- Compare results of modeled microgravity respiration to 1G respiration in an animal model including cardiac output, arterial venous pressure, lung volume and mechanics
- Compare results of modeled microgravity respiration to previous actual microgravity data from animal models
- Use radiographic imaging to measure pulmonary blood flow distribution, distribution of ventilation and other quantities that have not been previously measured
- Incorporate data into a model for human performance in microgravity

Glenn/JSC Bioreactor Collaboration

Optimize fluid transport of RWPV replacement to allow for bubble removal while still providing a well-mixed, low-shear environment for culturing cells.





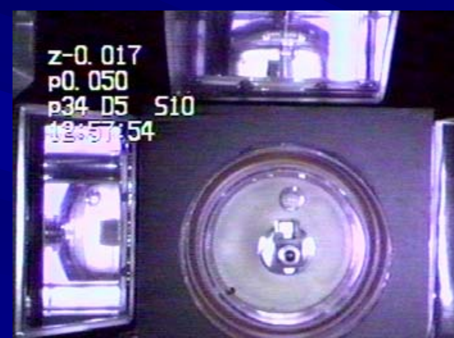
Hydrodynamic Focusing Bioreactor (HFB)

Proposed as a design that would allow for bubble removal from a central port.

Rotating Wall Perfused Vessel (RWPV)

Flown on STS-70, -79, -85, -89, and operational on NASA/Mir Increment 3 and 7.

Long term operation on Mir required external media replenishment, which allowed bubbles to enter the system that could not be removed.



KC-135 Experiment Results

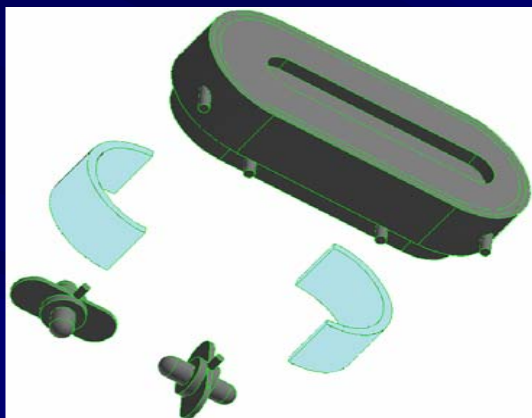
HFB shear levels and oxygen distribution are not as good as the RWPV, but bubble removal may be overriding concern.

KC-135 Apparatus

Used in HFB bubble mitigation and removal studies

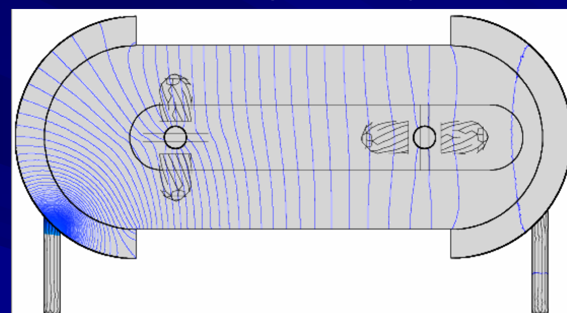
Glenn/ARC Cell Culture Unit Collaboration

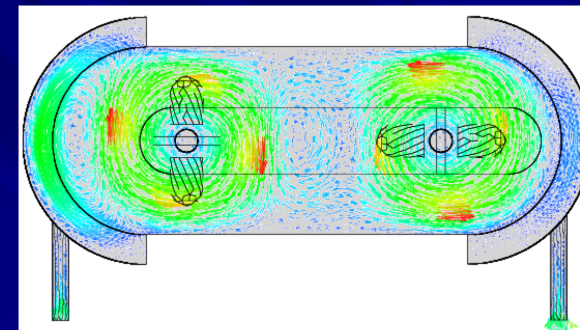
Optimize fluid homogeneity and minimize cell shear stress for various Cell Specimen Chamber designs and mixing protocols through use of computational fluid dynamic modeling and analysis.



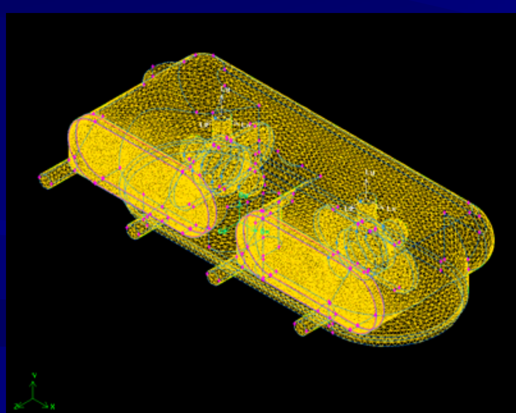
Geometry Definition
CFD models built from CAD three dimensional geometry

Isoconcentration Contours
Used for determination of homogeneity of chamber and flushing efficiency



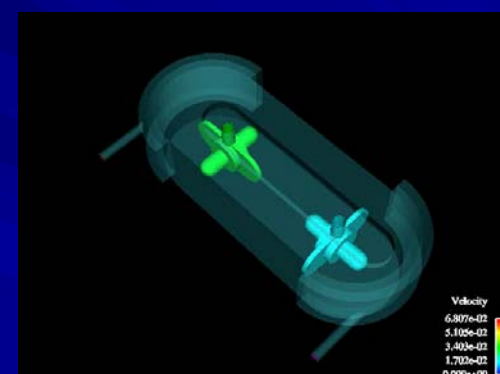


Velocity Field
Used for determination of uniformity in flow field



Mesh Generation

700,000 – 1,400,000 elements used in modeling and analysis



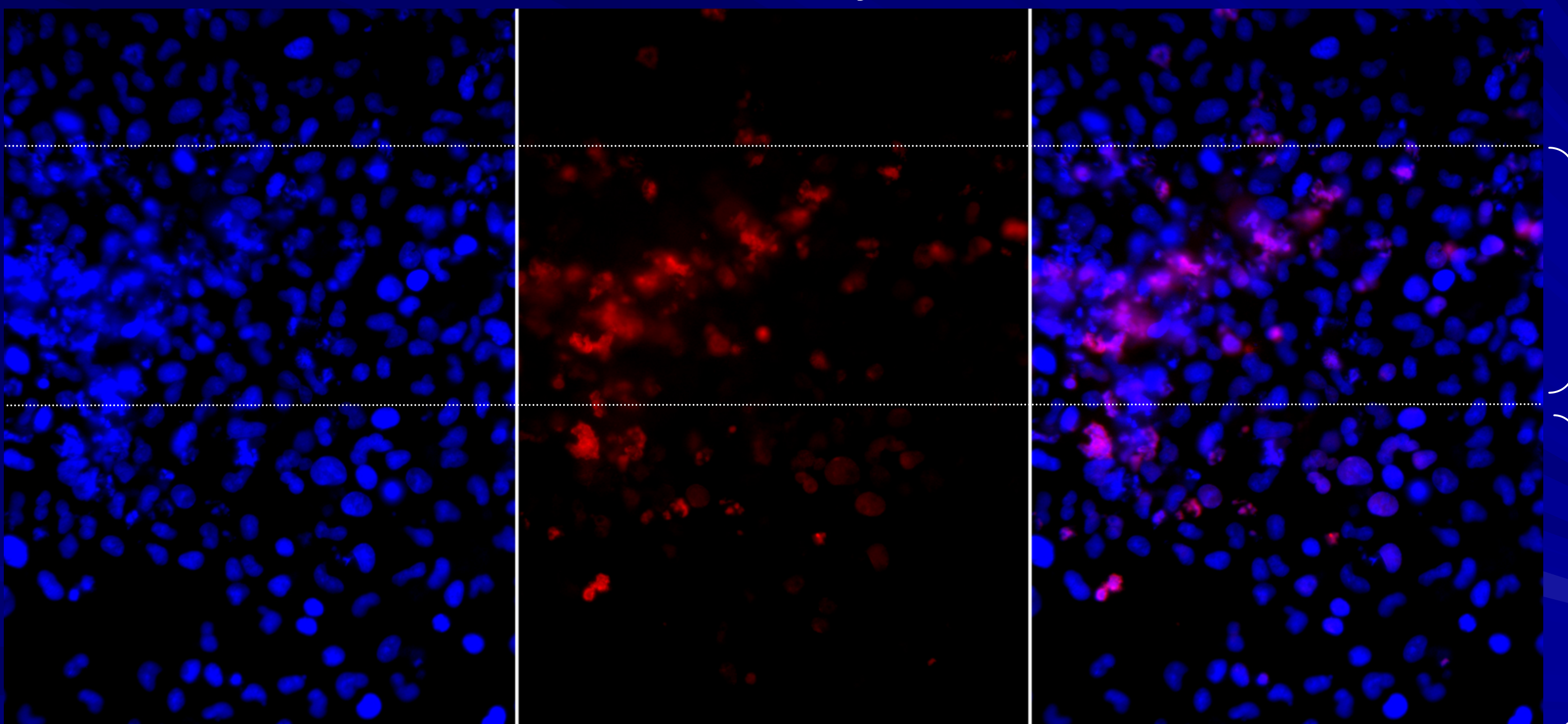
3D Simulations
Used for animation of CFD analysis results and verification of flow visualization studies

Effects of fluid flow on wound healing in bone. A BrdU assay developed by NASA GRC and the CCF.

DAPI only

Alexa Fluor 594, anti-BrdU only

DAPI + Alexa Fluor 594, image overlay

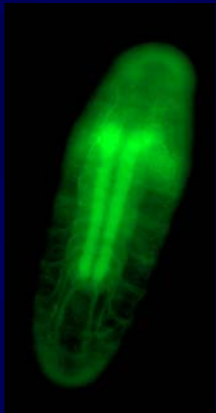


Confluent monolayer

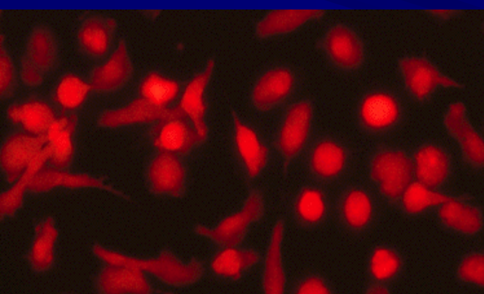
Scratch margin

Scratch cleft

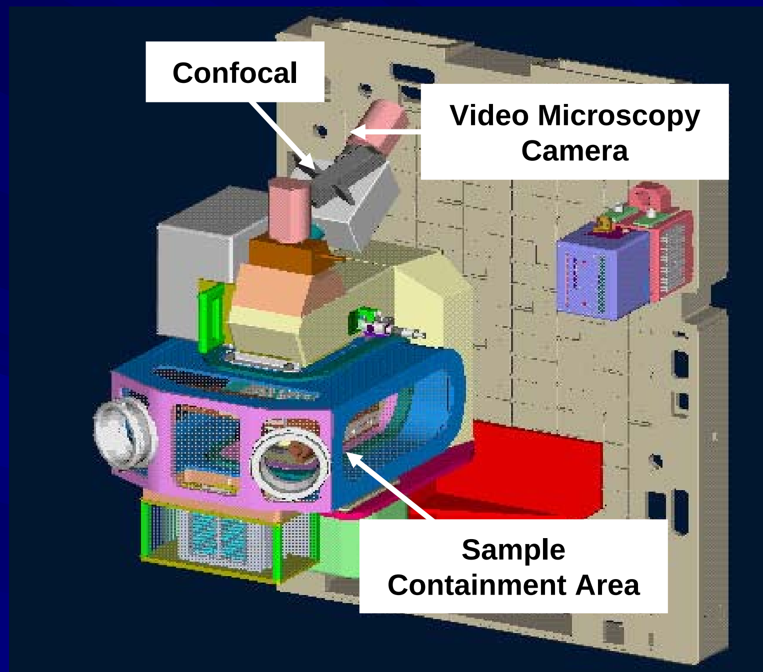
LMM Supports Bio Imaging

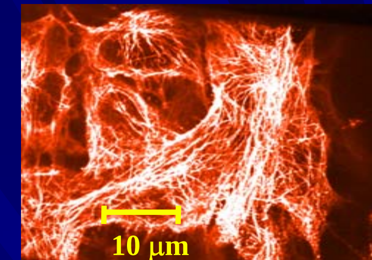


GFP image of Drosophila embryo imaged using LMM ground hardware
(sample courtesy ARC)



Human neutrophils (Molecular Probes)





Confocal image of rat actin imaged using LMM ground hardware
(sample courtesy of Nancy Searby, NASA ARC)

Key features:

- confocal and wide field fluorescence microscopy
- oil immersion system
- bright & dark field, phase contrast and DIC
- video microscopy
- thin film interferometry

Light Microscopy Module (LMM) is a remotely controllable, automated on-orbit microscope, allowing flexible scheduling and control of physical and biological science experiments within the Fluids Integrated Rack on the International Space Station.

Multidisciplinary Biomedical Research for Human Survival in Space

Overall Goals

- Understand the fundamental physical, chemical, and biophysical mechanisms that control human physiological behavior and performance.
- Delineate the effect of the space environment on the physiochemical and transport processes associated with human physiology
- Develop systematic countermeasures based on first principals to:
  - Assure human survival in space
  - Improve everyday clinical protocols on earth

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NCMR FLUIDS AND COMBUSTION

Multidisciplinary Biomedical Research for Human Survival in Space

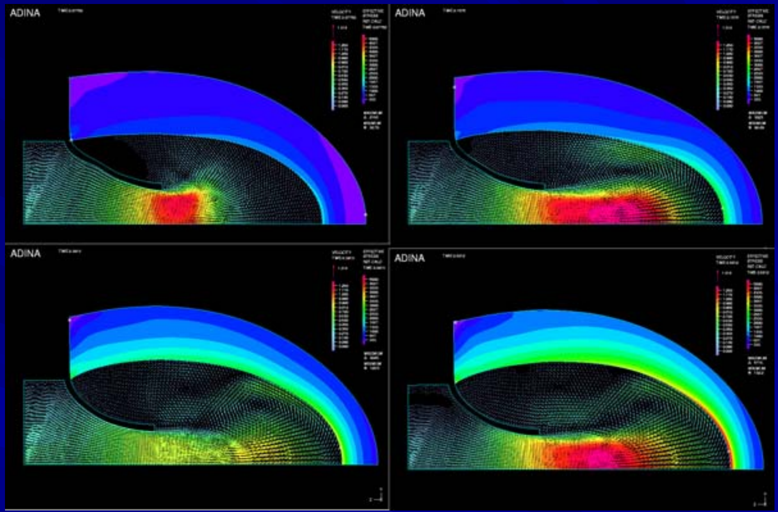
Examples of On-Going Projects

I. Variable Gravity Fluid-Structural Behavior of The Heart

Problem: Manifestation of cardiac dysrhythmia and asymptomatic cardiovascular disease in space

Approach: Study the intricate variable gravity Fluid-Structural Interactions (FSI) of the heart using 3D finite element model, animal experiments (zebra fish and dog), 3D MRI cardio-imaging, and clinical case studies.

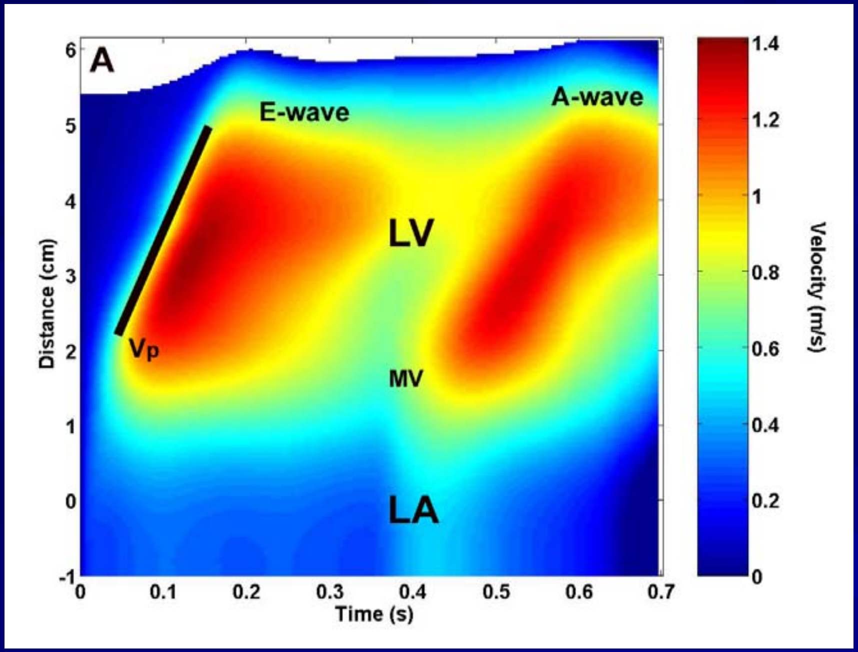
Outcome:
- Determine the effects of stress and transport conditions on cardiovascular development.
- Understand how lack of pericardial constraint in space can change cardiac pressure-volume relationships and how cardiac atrophy in microgravity can lead to a weakened heart - develop strategy for effective countermeasures.
- Determine the feasibility of using IntraVentricular pressure gradients as markers for early detection of diastolic dysfunction preceding congestive heart failure on earth.

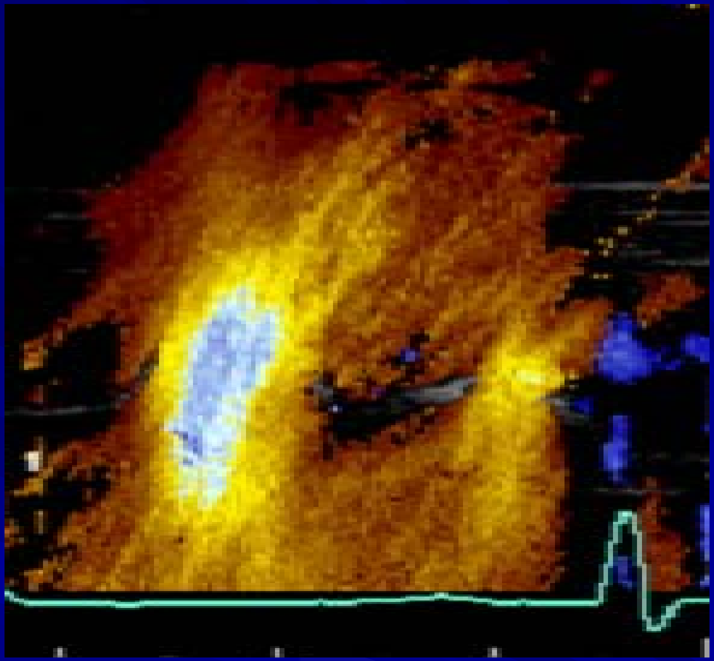


Flow & Stress During 1G Diastolic Expansion of Left Ventricle

Collaborators: CCF, CalTech, NCMR, GRC, CWRU, U. Leiden, U. Auckland, UCSD

Computational Cardiac Imagery
Color M-mode Doppler





Computational data

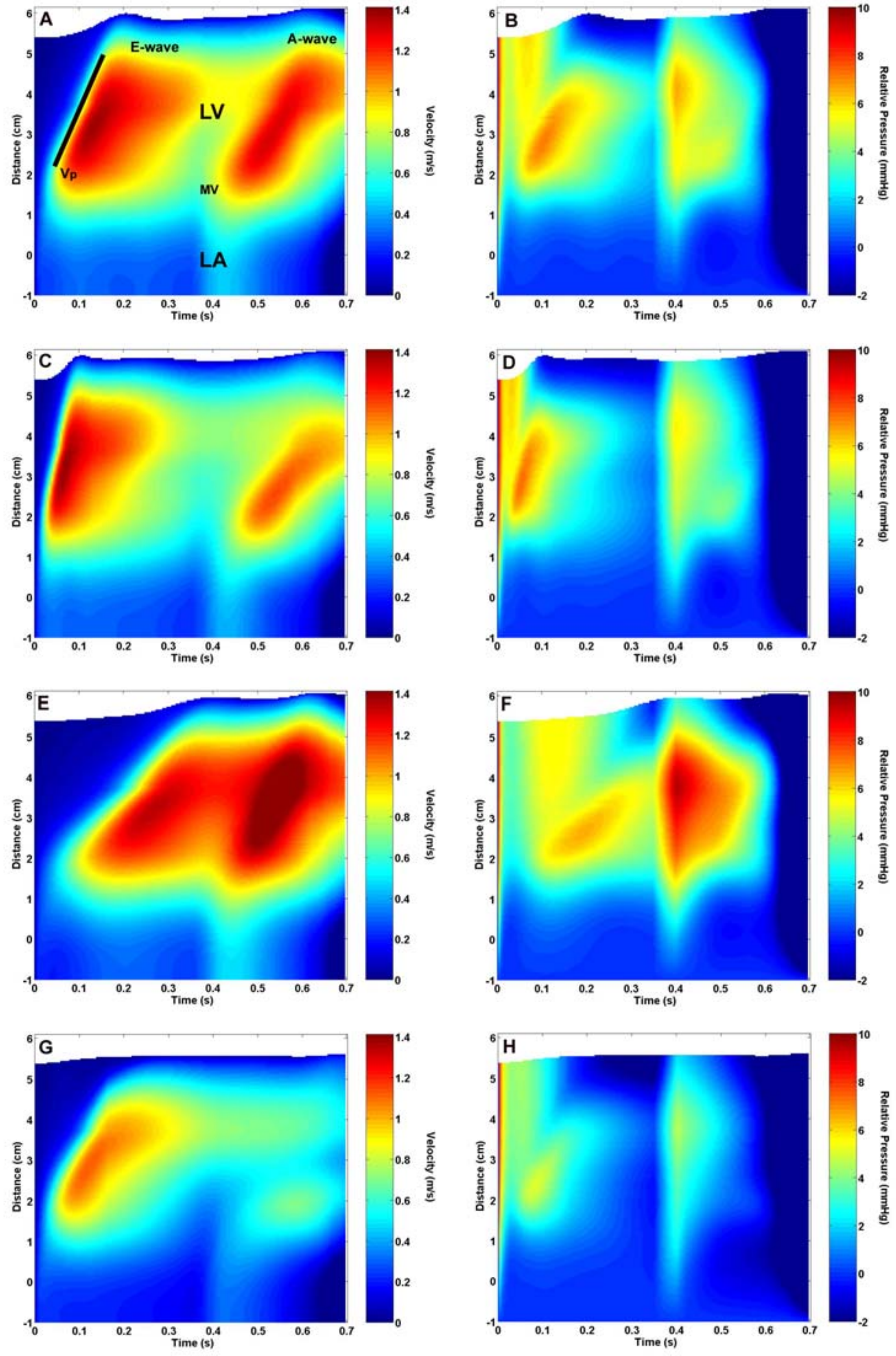
Clinical data (example)

Computational Cardiac Imagery Parameter Study

Increased relaxation rate

Decreased relaxation rate

Increased end-diastolic stiffness



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Multidisciplinary Biomedical Research for Human Survival in Space

Examples of On-Going Projects

II. Gravitational Physics of The Inner-Ear and Balance Disorders

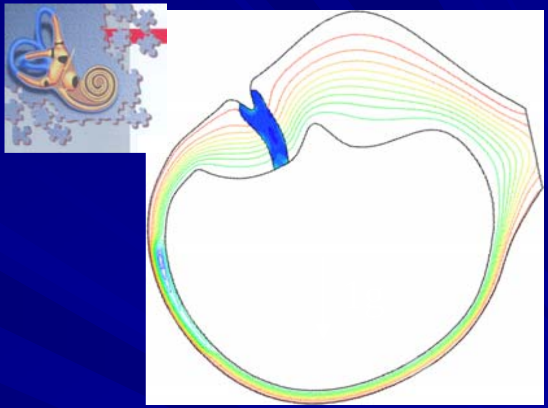
Problem: Disorientation and inability to perform required physical and mental tasks especially during and after g-level changes.

Approach: Study the fluid-structural interactions (FSI) in the Semi-Circular Canal (SCC) System of the inner-ear under 1g, weightlessness, and artificial gravity (AG) conditions of Short Arm Centrifuge (SAC) using a combination of numerical/theoretical models, physical experiments, animal models and clinical data.

Outcome:

• Recommend countermeasures based on first principal physics to reduce the risk of vestibular disorders arising from exposure to microgravity. Define systematic protocols for use of SAC based on correct understanding of the non-intuitive fluid mechanics of AG.

• Delineate the physical mechanisms responsible for common vestibular problems on earth such as Benign Paroxysmal Positional Vertigo (BPPV) or Unilateral Vestibular Loss (UVL).



Flow Bending the Cupula Partition

Collaborators: CCF, NCMR, GRC, CWRU , U. Washington, U.Utah

Interdisciplinary Research Strategy for Growth

- **Collaboration on proposals to NASA Research Announcements (NRAs) in bio-related areas**
- **Establish directed projects with tangible milestones and provide oversight**
  - Enhanced Light Microscopy Module/ Biological and Physical Research Rack
    - ✓ Memorandum of Agreement in place with ARC and with JSC
  - Microgravity fluid modeling for human physiology and advanced life support applications
  - Cell Culture Unit / Bioreactor hardware design
  - Technology development and demonstration for countermeasure development
- **Utilize the expertise at the National Center for Microgravity Research (NCMR) to enhance scientific capability for strategic research implementation**
- **Continuation of the John Glenn Biomedical Engineering Consortium**
- **Success of the NASA BioScience and Engineering Institute**
- **Joint interagency agreements – NIH/NASA**
  - Example: Computational modeling of human body with focus on bone loss

Bioscience and Engineering in NASA's Office of Biological and Physical Research

Summary:

- **NASA's research program is guided by the President's vision and the President's Management Agenda**
- **Current program emphasizes cross-discipline and interorganizational collaborations**
- **Images are both visual and computational**